TREATMENT AND MANAGEMENT OF HIV INFECTION IN THE UNITED STATES
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DHP CONFERENCE PERSPECTIVES

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With HIV More Treatable, Challenge Lies in Identifying Patients, Retaining Them in Care

With the development of highly active antiretroviral therapy (HAART), HIV infection has been transformed from a fatal disease to a chronic yet treatable condition; however, the effective long-term treatment of patients with HIV presents unique challenges that extend far beyond prescribing an antiretroviral regimen. The identification, diagnosis, and effective management of these patients require the cooperation of experts ranging from physicians, nurses, and pharmacists to social workers, counselors, and nutritionists.

The conference steering committee recognized the need for a venue to discuss topics such as prevention,

Victoria A. Cargill, MD

initial treatment, comprehensive care, and management of HIV-associated conditions. As steering committee chair Lawrence Deyton, MD, MSPH, explained, "Although most front-line providers cannot attend international research conferences, they want to apply the latest research findings into their clinical practices. We specifically targeted this conference to the practical, day-to-day management challenges that arise in the federally supported centers that are increasingly providing HIV care."

The Link Between HIV and Poverty in the United States

According to program committee co-chair Victoria Cargill, MD, MSPH, "HIV has always been a health disparity—a disease of poverty, unequal access to healthcare, and health illiteracy." Recent statistics

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Early Intervention, Team Effort the Key to Linking Patients with HIV Care

Community outreach, comprehensive services, and peer programs are key elements in identifying, engaging, and maintaining patients in HIV care, according to Wafaa El-Sadr, MD, MPH, of the Harlem Hospital Center and Columbia University in New York, NY. Her long-term involvement in the development of HIV testing and care programs in the New York area offers a valuable perspective to share with front-line providers across the country. She discussed various HIV testing programs, highlighted continuing disparities in HIV care, and suggested strategies to improve linkage to care.

Community Testing Programs Increase Access to Care

Dr. El-Sadr emphasized the importance of diagnosing HIV, particularly in individuals at risk, noting, "We have to reach outside the clinic walls and link with others in the community." Mobile vans offering HIV/sexually transmitted disease screening are one outreach option, and using rapid testing may enhance their effectiveness. In a study evaluating mobile service in a high-risk setting, 65% of clients preferred rapid testing over traditional testing (Liang

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The Challenge of HIV: Advances in Treatment, But Not Prevention

More than 20 years in HIV research and patient care allow John Bartlett, MD, a unique vantage point from which to critique the fight against the disease and where it is headed. "In the year 2010, you may say, 'Do you remember the year 2005 when we gave the triple regimen and thought it was a big deal?'" Genetics and the "incredibly rich" pipeline of new HIV drugs help fuel his optimism.

Indeed, Bartlett, the Stanhope Boyne Jones Professor of Medicine at the Johns Hopkins University of School

John Bartlett, MD

of Medicine, cautiously predicted these advances will generate a "quantum leap" in the care and treatment of HIV. Bartlett's sanguine view of the future was all the more remarkable considering the dizzying speed of HIV research and treatment in the last 15 years. Progress in the field already has generated unprecedented advancements in the quality of life for HIV patients.

"Most people can still remember the time when people got wasting disease, [now] you just don't see people who are desperately ill," Bartlett observed in comments before his talk. He is among those

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who do remember. He was the first to direct clinical trials in Baltimore, Md, of new treatments that prevent HIV from replicating. He pioneered the development of dedicated inpatient and outpatient medical care for HIV-infected patients.

Table 1. Survival Gains

Intervention	Per Person Survival Gain (months of life gained)
Cancer chemotherapy	10
Coronary bypass surgery	20
HAART-HIV	100

HAART = highly active antiretroviral therapy.

Reprinted with permission from Walensky RP, et al. 12th Conference on Retroviruses and Opportunistic Infections 2005. Abstract 143.

A recent analysis of life expectancy for patients with HIV infection revealed that incremental improvements in HIV care in the last 15 years now provide approximately 180 additional months of life per person, compared with an additional 10 months afforded by cancer chemotherapy and 20 months for coronary bypass surgery (Table 1; Walensky RP, et al. CROI 2005. Abstract 143). Applied across those affected by HIV, researchers posited an estimated cumulative gain of 2 million life-years in the United States (Table 2). Extrapolating the analysis to Africa, there would be a cumulative gain of 2 billion life-years.

Bartlett was further encouraged by early reports on the chemokine receptor (CCR5) that regulates leukocyte chemotaxis activation, blocking entry of the virus into the cell. This mechanism of action contrasts to that of most existing drugs, which work inside the immune cells. Bartlett portends a complete change in the approach to therapy.

Genetics also is becoming a significant factor in HIV infection. Bartlett predicted the focus will intensify on the natural history of those with and without HIV infection. He cited reports of sex workers who had repeated, unsafe exposure over the course of 10 years, yet did not develop the disease. Even more intriguing is that family members seemed to show similar protection against the disease. Genetics may also help explain why two people found to be infected with the same viral strain in New York City recently differed vastly in their response to therapy. While one decompensated rapidly from infection to end-stage disease in a matter of months, the person's sexual contact, who had been infected in 1995, was alive and doing well. Bartlett observed that the rate of replication of the virus is likely dependent on the host immune system. How such "long-term nonprogressors" thrive has significant implications on the direction of AIDS vaccines.

Bartlett's nagging disappointment in the fight against HIV is the dismal failure of prevention efforts. "In 1990, we had 40,000 new cases of HIV; in 2004, we had 40,000 new cases. We've had great success with therapy; as far as I can tell, we've gone no place with prevention." Bartlett thinks the key to prevention might be in finding and counseling newly infected persons during the highly infectious period when they are antigen–positive and antibody–negative. He was intrigued by data from Uganda suggesting that most HIV transmission takes places within 3 months of a new infection. Thus, the challenge lies in recognizing the early stage of infection and identifying persons who are in it.

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Table 3. Cost of Antiretrovirals

Agent	Regimen	AWP ($)	Cost per day($)	Cost per month ($)
TPV	500 mg bid	8	32	900
RTV	200 mg bid	11/2	8	240
T20	90 mg bid	34	68	2100
TOTAL			$108	$3240

TPV = tipranavir; RTV = ritonavir; AWP = average wholesale price.

Bartlett hoped that the HIV community will pay greater attention to unconventional HIV prevention strategies, such as diaphragms, circumcision, and prophylaxis with antiretrovirals. Bartlett was encouraged by the development of rapid HIV testing, which can help researchers identify early infection by eliminating a person's need to make two or more visits to determine HIV status.

The combination of success in treatment and failure in prevention combine to produce another challenge for HIV clinicians: the exploding cost of HIV antiretroviral therapy. The average annual treatment cost of $38,000 to $51,000 is straining existing financial resources such as the federal Ryan White program (Table 3). "It's rare for me to find a provider in the United States who knows anything about the cost of HIV drugs, but we're going to have to start paying attention," Bartlett warned. ●

Table 2. Cumulative Benefit of HIV Care

Year	Treatment	Patients x 1000	Survival (months)	Total (years)
1989-92	PCP prophylaxis	113	2	18
1993-96	MAC prophylaxis	162	5	3
1997-98	ART-1	79	40	265
1998-99	ART-2	53	105	504
2000-02	ART-3	78	111	723
2003	ART-4	27	179	409
TOTAL LIFE-YEARS GAINED				2,101,232

ART = antiretroviral therapy; MAC = mycobacterium avium complex;
PCP = pneumocystis carinii pneumonia.
Reprinted with permission from Walensky RP, et al. 12th Conference on Retroviruses and Opportunistic Infections 2005-Abstract 143.

Table 1. Resistance Testing in Treatment Naïve Patients

- Resistance testing always indicated for acute or recent infection
- Growing support for resistance testing in chronically infected, treatment-naïve patients
- Despite persistence of mutations, yield is highest with earlier testing;
  - Test at time of diagnosis, regardless of need for therapy
- Genotype preferred: more sensitive for detection of mixtures

Detection, Observation Skills Crucial in Diagnosis, Initial Evaluation of Patients with HIV

Although much emphasis in HIV medicine is placed on the effective use of antiretroviral therapy, caring for patients with HIV begins with their first office visit. HIV clinician, researcher, and educator Joel Gallant, MD, MPH, associate professor of medicine and epidemiology, Johns Hopkins University School of Medicine and associate director of Johns Hopkins AIDS services, Baltimore, Md, discussed the identification and diagnosis of HIV infection and reviewed components of the initial evaluation of patients with HIV.

Benefits of Early Detection

Patients with undiagnosed HIV may arrive for an initial consultation at any stage of the natural history of untreated HIV infection. Clinicians must therefore be prepared to identify HIV-related complications that may occur at different CD4 cell counts. Gallant noted, "It is critical when seeing patients for the first time to find out where they fit on the HIV natural history curve. This assessment is also important for establishing a differential diagnosis." Additionally, CD4 cell counts can be used to assess the need for prophylaxis against opportunistic infections.

Gallant reminded clinicians of the value of diagnosing primary HIV infection for explaining the patient's symptoms, preventing further transmission, and obtaining a timely resistance test (Table 1). "Although primary HIV infection is symptomatic in most patients, in most cases the diagnosis is missed." Common clinical presentations include fever, lymphadenopathy, pharyngitis, erythematous maculopapular rash, and myalgias/arthralgias (Fauci AS, et al. *Ann Intern Med.*

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show that 71% of new HIV cases in the United States occur in minorities, and 67% of newly infected women are African-American (Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report,* 2003. 2004;15). For many patients with HIV, social services are therefore an integral part of total care.

Barriers to HIV Detection and Open Communication

The first step in the treatment of HIV is making individuals aware of their infection. Emergency departments (EDs) have been promoted as potential avenues for testing, and several studies have demonstrated that routine HIV testing in EDs is feasible (Rothman RE, et al. *Acad Emerg Med.* 2003;10:278-285). However, the transient nature of most ED interactions presents challenges for follow-up. On the other hand, the perceived stigma surrounding HIV may remain a barrier to HIV detection by health care professionals with close relationships to the individual. Cargill explained that a person may hesitate to discuss high-risk behavior with the primary care physician; consequently, the testing is not done.

Cargill noted that the threat of being stigmatized can negatively affect patients. Individuals who do not disclose their HIV status and current antiretroviral regimen to other healthcare providers may be prescribed medications that interact with antiretroviral agents, resulting in drug interactions (Tseng AL, et al. *Ann Pharmacother.* 1999;33:461-473). Front-line providers can help by asking about high-risk behaviors and encouraging communication. Deyton added, "We should empower front-line providers by making HIV testing easier and more routine. HIV testing should be normalized, but not minimized."

"HIV has always been a health disparity— a disease of poverty, unequal access to healthcare, and health illiteracy."

Challenges in Adherence

Program committee co-chair Paul Volberding, MD, MPH, discussed the importance of learning how to effectively promote adherence. "The responsibility of adherence is shared between the provider and the patient," he said. "Building a system that supports adherence is essential to the success of the treatment, because in no other field of medicine does adherence have to be as scrupulous as with HIV."

Research indicates that solid patient-provider relationships are integral to adherence. Malcolm and colleagues examined attitudes of patients with HIV/AIDS who had "excellent adherence" to therapy. They found that patients with excellent adherence trusted their providers, remained adherent despite substance abuse, had a social support system, and were not actively depressed (Malcolm SE, et al. *AIDS Care.* 2003;15:251-261). Cargill explained that patients "need a place where they feel comfortable with providers and can seek help with life situations such as depression, substance abuse, or a chaotic lifestyle." At that point, patients are better equipped to adhere to treatment.

Paul Volberding, MD (left); Lawrence Deyton, MD (right)

HIV-Related Co-infections and Malignancies

The nature of HIV-related complications has changed from the early years of HIV, when opportunistic infections were common. Today, HIV-related complications and malignancies still occur, with varying frequency depending upon the patient population. Hepatitis C co-infection, for example, is highly prevalent among intravenous drug users (CDC Fact Sheet. September 2002. Available at: http://www.cdc.gov/idu/hepatitis/viral_hep_drug_use.htm). A 2001 report showed that 40% of all patients treated at an HIV clinic in San Francisco were HCV-positive; although significantly higher rates have been noted in high-risk populations (Hare CB, et al. Program and Abstracts from a meeting of the American Association for the Study of Liver Diseases. November 9-13, 2001. Dallas, TX. Abstract 1258; Sherman KE, et al. *Clin Infect Dis.* 2002;34:831-837). Hepatitis C can result in severe morbidities, since infected patients cannot tolerate antiretroviral therapy.

Prevention Efforts Focus on HIV-Positive Individuals

Based on the notion that every new case of HIV begins with someone who is already infected, the "Prevention for Positives" initiative aims to stop the transmission cycle by increasing individuals' awareness and sense of responsibility for preventing transmission. Behavioral interventions have been shown to reduce high-risk behavior (Kalichman SC, et al. *Am J Prev Med.* 2001;21:84-92). However, an exit survey of patients leaving primary HIV clinics found that only 25% had discussed prevention with their provider at that visit, and only 6% discussed specific sexual activities. Prevention counseling was significantly less common than counseling for other social and medical issues ($P < .001$) (Morin SF, et al. *J Acquir Immune Defic Syndr.* 2004;36:960-966). Front-line providers can assist in this effort by discussing prevention routinely with their patients.

Effective HIV care requires a holistic team approach that draws upon providers with a wide range of skills to address the various needs of patients. This inaugural HIV treatment and management conference offered front-line providers practical education and a venue in which to exchange ideas and make connections to make their practices even stronger. ●

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Intermittent HIV Viremia "Blips" Not Clinically Significant

Consider hanging on to an existing, though imperfect, HIV antiretroviral regimen if it maintains a patient's viral load of less than 20,000 copies and a minimum CD4 T-lymphocyte count of 50. That is the yardstick that emerged from several cohort studies on the management of antiretroviral regimens in treatment-experienced patients, noted Roy Gulick, MD, MPH, associate professor of medicine and director of the Cornell University HIV Clinical Trials Unit. Gulick cautioned that the ultimate decision on whether to switch antiviral strategies should incorporate indicators from a patient's history as well as a subjective evaluation of the goals of therapy. At the same time, he acknowledged the cost of continuing a regimen in the presence of persistent viremia: continued selection for resistant viral strains.

Gulick's suggestion to give the benefit of the doubt to existing therapeutic regimens is admittedly more liberal than current Department of Health and Human Services (DHHS) recommendations that suggest switching therapy in the event of an incomplete virologic response (ie, a viral load greater than 400 copies/mL by 24 weeks or greater than 50 copies/mL by 48 weeks) (Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents.* Available at: www.hivatis.org). (See Table.)

Table. When to Change Therapy?

- **Virologic failure**
  - Incomplete virologic response (HIV RNA >400 cpm by 24 weeks or >50 cpm by 48 weeks)
  - Virologic rebound (after suppression, recurrent viremia)
- **Immunologic failure**
  - Failure to increase CD4 cell count by 25-50 over 1st year
  - Decrease to below baseline
- **Clinical failure**
  - Occurrence/recurrence of HIV-related events (excluding immune reconstitution syndromes)

DHHS Guidelines, April 7, 2005

In support of a more liberal strategy, Gulick pointed to the findings of a prospective observational cohort study (Ledergerber. *Lancet*. 2004;364:51-62). In 628 patients with stable HIV, CD4 counts increased so long as the viral load was suppressed to less than 10,000 copies/mL. The cohort also provided a credible guideline for a CD4 standard. The hazard of death increased 16-fold when the CD4 count declined from greater than 200 to less than 50 copies/mL (or less than 1.5 log10 copies/mL below baseline levels). Conclusions from this study were similar to those made by the DHHS, which conceded defeat of an antiretroviral therapy when CD4 counts did not exceed 50 in the first year of therapy or declined to baseline levels. The strongest support for adhering to a less than perfect antiretroviral regimen came from the experience of patients who maintained a viral load of 400 to 40,000 copies/mL. Although their CD4 counts did not increase as much as those with viral loads of less than 400 copies, their clinical progression did not differ from those with complete viral suppression.

Thus, for patients and providers weighing treatment options when no clear direction is provided by the presence of opportunistic infections or by virologic or immune system indicators and when a patient has few or no other antiretroviral options, a viral load of 10,000 to 20,000 copies/mL and a CD4 count of greater than 50 to 100 support continuing with the current regimen.

The call for resistance testing is becoming increasingly important, "and the best time for such testing is before starting any retroviral therapy," Gulick maintained. He further recommended considering routine resistance testing whenever the level of a resistant mutation in the community reaches 5%. Gulick attempts to reassurance to patients and providers who are worried about "blips," those inexplicable spikes in viral load that seem unrelated to progression in disease state or treatment regimen.

Intensive monitoring of a set of Johns Hopkins patients with a suppressed viral load showed that 9 of 10 patients experienced

Pharmacokinetic Variability in HIV Drug Regimens

Genetic and environmental variables in an HIV drug regimen contribute to the challenge of pharmacokinetic variability in which a given dose does not produce the same concentration in every individual. Fortunately, an exploding body of literature on drug interactions allows clinicians to tailor a medication regimen for individual patients, noted Angela Kashuba, PharmD, associate professor of pharmacy at the University of North Carolina, Chapel Hill. "Part of the issue we have when trying to predict drug interactions is that these are graded responses; it is not an all or nothing response," Kashuba observed. Numerous factors, such as drug-food interactions, drug-drug interactions, and different physiologic states, can accentuate drug reactions. In addition, polypharmacy dramatically increases the likelihood of interactions between any two drugs.

Kinetic interactions affect the concentration of drugs in the body through changes in absorption, distribution, metabolism, or elimination, while pharmacodynamic interactions are antagonist, synergistic, or additive. The P450 enzyme system, found mostly in the gut and liver, drives the majority of drug interactions. One significant emerging drug interaction has resulted in a 50% decline in concentrations of both zidovudine and abacavir when used in combination with tipranavir. "This isn't the first time we have seen protease inhibitors cause a decline in nucleoside concentration, but it has never been explored to any great extent," Kashuba said. Studies are underway that will allow clinicians to assess the clinical significance of these interactions.

When a regimen is discontinued, the persistence in the body of a single long-lived medication such as efavirenz poses the risk of resistance associated with monotherapy.

Clinicians must also cope with variations in the half-life of all drugs within a multidrug regimen. When a regimen is discontinued, the persistence in the body of a single long-lived medication such as efavirenz poses the risk of resistance associated with monotherapy; however, these risks can be minimized by using pharmacologic principles tailored to the individual clinical situation. Kashuba offered one possible strategy: stop the NNRTI and replace it with a protease inhibitor to "cover the tail end" of the half-life.

The presentation slides from the Treatment & Management of HIV Infection in the U.S. Conference are available for viewing at

www.ushivconference.org

The conference posters are also available online.

The call for resistance testing is becoming increasingly important, "and the best time for such testing is before starting any retroviral therapy."

intermittent episodes of detectable viremia. The blips usually were discordant (two separate laboratories frequently disagreed on whether a blip had occurred) and of low magnitude (median of 79 copies/mL). The blips were not associated with demographic or clinical factors, adherence, treatment, or drug resistance. These and similar results led researchers to conclude that the blips represented random, biological or statistical variation and were not clinically significant.

Therapy should be determined by the goals of treatment and patients' clinical status. For treatment-naïve patients, the clinical consensus remains maximum virologic suppression. For patients who have had extensive prior antiretroviral therapy, the DHHS recommends preserving immune function and avoiding clinical progression of disease; however, clinicians and researchers are rethinking the optimal strategies for treatment-experienced patients. The goal may well be to achieve virologic suppression with current agents and then switch to new agents as they become available. It is essential, however, to perform resistance testing while patients are on therapy and to identify susceptible drugs and drug classes. ●

Resistance Testing Helps Identify Optimal Treatment Regimens

Resistance testing is a crucial tool in the quiver of clinicians seeking to target optimal treatment regimens for treatment-experienced HIV patients, maintained Daniel Kuritzkes, MD, associate professor of medicine at Harvard University School of Medicine and director of AIDS research at Brigham and Women's Hospital.

Kuritzkes shared recent International AIDS Society guidelines on clinical situations that call for resistance testing (Hirsch et al. Clin Infect Dis. 2003;37:113-128):

- Acute or recent (within 12 months) HIV infection
- Before initiation of antiretroviral therapy in established HIV infection
- First regimen failure
- Multiple regimen failure
- Pregnancy (in mothers with detectable plasma HIV-1 RNA levels)

"The cynics will note that this list actually recommends testing in virtually all imaginable scenarios, and that's true," Kuritzkes conceded. "The indications for resistance testing are becoming more and more thorough."

Resistance testing, however, has its limitations. For example, in genotypic testing—by far the more common of the two kinds of resistance testing—drug resistance is inferred by the presence of known mutations and, therefore, is only as good as knowledge of critical mutations unearthed during development of the drug. Kuritzkes warned that resistance testing cannot be used to diagnose treatment failure: it is more accurate in assessing resistance to a current regimen. Lack of resistance to a previously used drug does not rule out reservoirs of resistant virus that might emerge after re-initiation of the drug.

For these reasons, Kuritzkes does not recommend using a drug that has shown to be resistant at any time, even if current test results suggest susceptibility. The good news for clinicians is that resistance is rarely absolute. Many drugs retain at least partial antiviral activity, and resistance assays do not account for the activity of drugs used in combination.

"Very often it is possible to cobble together a regimen that is at least partially active by using several drugs and still get a meaningful clinical response," Kuritzkes noted. In addition, pharmacologic enhancement can compensate for resistance to some protease inhibitors. Kuritzkes counseled clinicians to continue to experiment with treatment regimens when resistance or other challenges. "It is important to persist with therapy even in the face of failure. Persistent viral replication may lead to immunologic decline, but..., some treatment is better than no treatment at all."

Addressing Patients' Needs Helps Promote Adherence to Antiretroviral Therapy

For clinicians treating patients with HIV, promoting adherence to antiretroviral therapy is an important task that involves education, relationship building, and understanding a patient's life situation and needs, according to Laura Cheever, MD, chief medical officer and deputy director of the HIV/AIDS Bureau at the Health Resources and Services Administration. Cheever reviewed the challenges of promoting adherence, particularly among patients with substance abuse issues.

In discussing long-term adherence, Cheever spoke of a continuum of engagement of care, which ranges from individuals unaware of their HIV status at one end of the spectrum to those who are fully engaged in HIV primary medical care at the other end. "In between," she explained, "we have many types of patients, including those who never seek HIV care and those in and out of care. In this country, we spend a lot of resources getting patients tested and into care, but we haven't done enough for patients in the middle of this continuum."

... substance abuse is a chronic condition, relapses will happen, so clinicians should expect them. View them as a time to intensify treatment, not as failure.

Overall, today's simplified drug regimens make adherence much easier; however, personal issues such as substance abuse and life situations can play a central role in a patient's likelihood to adhere to treatment. Cheever cited a prospective study of 764 HIV-infected patients attending an urban HIV clinic, which found that active drug users (44%) were significantly less likely than former users (22%) or nonusers (18%) to adhere to an antiretroviral regimen (Lucas GM, et al. *J Acquir Immune Defic Syndr.* 2001;27:251-259). Active drug use was significantly associated with fewer virologic and immunologic improvements from baseline.

In a prospective study of injection drug users, a higher proportion of patients on methadone maintenance therapy (MMT) adhered to an antiretroviral therapy regimen after 2 years (70% vs 44% of patients not on MMT; log-rank $P = .001$) (Wood E, et al. AIDS. 2005;19:837-839). Other support services, such as case management, transportation services, and mental health care, can increase a patient's long-term retention in care by addressing their unmet needs (Sherer R, et al. *AIDS Care.* 2002;12(suppl 1):S31-44).

Cheever stressed the importance of educating patients about the risks of developing resistance that come with suboptimal adherence (Bangsberg DR. *AIDS*. 2000;14:357-366). She described a patient who had dropped out of care for 6 months. "The patient and I had had that important discussion about resistance and adherence, so when she started regularly missing doses, she stopped all of her antiretroviral therapy. When I saw her 6 months later, she did not have any resistance mutations."

Research shows that treatment discontinuation is common. In a cohort of 936 women, 24% of patients discontinued all antiretroviral therapy for at least 6 months during a 5-year follow-up (Ahdieh-Grant L, et al. *J Acquir Immune Defic Syndr.* 2005;28:500-503). Although reasons for discontinuation may vary, commonly sited reasons include depression (Ahdieh-Grant L, et al. *J Acquir Immune Defic Syndr.* 2005;28:500-503), toxicities (O'Brien ME, et al. *J Acquir Immune Defic Syndr.* 2003;34:407-414), patient choice (Mocroft A et al, *AIDS Res Hum Retroviruses.* 2005;21:527-536), and injection drug use (Moss AR, et al. *Clin Infect Dis.* 2004;39:1190-1198).

In addressing these issues with patients, Cheever recommended that clinicians avoid being judgmental and instead view substance abuse as a health problem rather than a social dilemma. "Because substance abuse is a chronic condition, relapses will happen, so clinicians should expect them. View them as a time to intensify treatment, not as failure," she added. "There is a lot we can do for these patients; however, substance abuse is a chronic illness that requires chronic treatment." ●

Detection, Observation Skills Crucial in Diagnosis, Initial Evaluation of Patients with HIV

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1996;124:654-663).

Determining viral resistance is important, and testing is best done during acute infection. Gallant noted, "Resistance testing should be done at the time of diagnosis, regardless of the need for therapy. Sooner or later, the patient will start therapy, and the yield is highest with earlier testing." In a recent multisite study, 15% of newly diagnosed, ART-naïve individuals exhibited some drug resistance, and 3% were resistant to at least 2 drug classes (Bennett D, et al. Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston, Mass. Abstract 674). Genotype resistance testing is the preferred method, as it is more likely to detect mixtures of wild-type and mutant viruses.

Making an HIV Diagnosis

Gallant mentioned several indications for voluntary HIV testing (Table 2); however, he noted, "There is growing support that HIV testing should be routine, especially for sexually active adults." In addition to clinical manifestations, laboratory abnormalities common to HIV-infected individuals include anemia, leukopenia, and thrombocytopenia (Moroni M, et al. *AIDS*. 2003;17 (suppl 1):S51-64).

Clinicians suspecting primary HIV infection should request both antibody-based and nucleic acid-based tests to gauge a patient's status. Individuals with negative/indeterminate serology and high positive viral load (>100,000 copies/mL) are likely to have primary HIV infection, while individuals with negative serology and low viral loads can have false positive results (Daar ES, et al. *Ann Intern Med*. 2001;134:25-29).

Components of the Initial Visit Following an HIV Diagnosis

The initial history and physical examination can reveal important information regarding the estimated time of infection and potential exposure to other pathogens, including sexually transmitted diseases, hepatitis, tuberculosis, and chicken pox/shingles. Travel histories may also reveal potential exposure to endemic pathogens (Kasten MJ. *Mayo Clin Proc*. 2002; 77:957-962).

Important components of the physical examination include evaluations for HIV-related oral conditions, lymphadenopathy, hepatosplenomegaly, anogenital warts and ulcerations, and neurologic disorders (Kasten MJ. *Mayo Clin Proc*. 2002; 77:957-962). Furthermore, a thorough review of systems can reveal clinical depression and coping problems that might affect adherence to therapy.

Gallant noted that obtaining a family history is important for assessing a patient's risk for developing diabetes and early coronary artery disease, conditions that may be affected by antiretroviral therapy. In addition to family history, a social history should be taken to assess an individual's living situation, sexual history, and potential for substance abuse, and to aid in disclosing the infection to exposed partners. The medication history should include use of over-the-counter medications and herbal therapies.

It is important that front-line providers continue to seek the resources required to provide effective care and that non-HIV experts maintain some involvement with an HIV expert in order to provide the best care for their patients.

In addition to confirming the HIV diagnosis, baseline laboratory evaluations should include HIV genotyping; a chemistry panel; screening for sexually transmitted disease, viral hepatitis, and toxoplasma; and lipid testing. In some patients, urinalysis or screening for varicella, cytomegalovirus, or glucose-6-phosphate dehydrogenase deficiency might be indicated. Symptomatic patients may require additional tests according to their CD4+ cell count (Kasten MJ. *Mayo Clin Proc*. 2002;77:957-962). Finally, baseline and periodic vaccinations should be administered as appropriate. Immunocompromised patients should defer vaccines until immune reconstitution occurs.

Next Steps

An important aspect of linking patients to care is recognizing the need to refer patients to outside services such as gynecology, nutrition, social services, mental health services, substance abuse programs, and ophthalmology (Kasten MJ. *Mayo Clin Proc*. 2002;77:957-962).

Gallant concluded by emphasizing the importance of providing expert care. He observed that "an HIV expert is not necessarily an infectious disease specialist, and vice versa. Expertise is generally defined by experience and continuing medical education." It is important that front-line providers continue to seek the resources required to provide effective care and that non-HIV experts maintain some involvement with an HIV expert in order to provide the best care for their patients. ●

Table 2. Indications for Voluntary HIV Testing

- STDs
- Pregnancy
- Tuberculosis
- Recurrent pneumonia
- Refractory/recurrent vaginal candidiasis
- Generalized lymphadenopathy
- Unexplained dementia, aseptic meningitis, or peripheral neuropathy
- B-cell lymphoma
- Chronic, unexplained fever, diarrhea, or weight loss
- Shingles (young adults) or generalized HSV
- Unexplained cytopenias
- Evidence of cellular immunodeficiency
- Hospitalized adults (if AIDS rate >1/1000 discharges or seroprevalence >1%)

. . . or upon request

STDs = sexually transmitted diseases; HSV = herpes simplex virus.

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TS, et al. *AIDS Patient Care STDS*. 2005;19:253-257). Post-test counseling was also more likely to occur with the rapid test. Among clients with a positive test result, the counseling rate was 89% following the rapid test, compared with 11% of clients who chose the traditional test (Table).

In a randomized study evaluating community outreach at needle exchange programs and bathhouses, traditional and rapid testing were offered at randomly determined dates. Of 7041 eligible individuals, 761 (11%) were tested. Rapid testing was significantly preferred over traditional testing, and it was associated with a significantly higher frequency of individuals receiving their test results at both locations (Spielberg F, et al. *J Acquir Immune Defic Syndr.* 2005;38:348-355).

El-Sadr suggested public hospitals as another important avenue for HIV testing. In a 2002 study that offered HIV counseling and testing for inpatients, 6.4% of all medical admissions were tested, representing a greater than 3-fold increase over the historical referral rate of 2%. A total of 3.8% of patients who historically would not have been tested were found to be HIV-positive (Walensky RP, et al. *Arch Intern Med.* 2002;162: 887-892).

According to steering committee Chair Lawrence Deyton, MD, "Undiagnosed patients are the tragedy in the current era. They are high-risk, they interact with the health care system, and they are not offered testing. We know that with delayed diagnosis, therapy may not be as effective. Also, the number one factor driving infection rates is people who don't know they're infected."

The period of primary infection, during which the risk of transmission is high, presents a challenge for identifying HIV-positive individuals and linking them with care; however, while primary HIV infection is usually associated with clinical symptoms, the diagnosis is often missed, resulting in several important failed opportunities. The HIV-positive individual is not able to immediately enter care and thereby optimize clinical outcome (Xiridou M, et al. *AIDS.* 2004; 18:1311-1320).

Facilitating Linkage to Care

While front-line providers now view HIV as a chronic, treatable condition, many HIV-positive individuals fail to receive treatment for a variety of reasons. El-Sadr suggested that fear and stigma, substance abuse, mental illness, lack of availability of care, expense, and distance are barriers to treatment. Several intervention strategies have been shown to lower or eliminate these barriers. In a 2005 randomized clinical trial, Gardner and colleagues recruited 318 HIV-positive individuals not in care and not receiving antiretroviral therapy, and evaluated the benefit of a case management program (*AIDS.* 2005; 19:423-431). For 3 to 5 sessions, individuals were counseled, encouraged to seek treatment, and escorted to clinic, if needed.

Case management was associated with more successful linkage to care (OR, 1.41; $P = .006$) compared with standard of care treatment consisting of information and passive referral. El-Sadr noted, "This highlights how one-on-one individual relationships are so critical for achieving any outcome." Peer counseling programs, based on the notion that a person with HIV can best reach another person with HIV, are also important tools for recruiting patients into care. El-Sadr helped to establish a peer program in her community that provided HIV counseling and testing, support and encouragement, navigation to services, and outreach. "The power of peers is underutilized," she explained. "Peers can accomplish what a clinician cannot. They provide support and communication, and help navigate these individuals into care."

Disparities in Treatment

El-Sadr noted that in this country, certain populations fail to receive proper HIV care. A 2005 study of individuals treated at HIV primary care sites showed that after adjusting for care site in a multivariable analysis, women and African Americans were less likely to receive antiretroviral therapy (Gebo KA, et al. *J Acquir Immune Defic Syndr.* 2005;38:96-103).

Access to experienced providers is known to significantly increase survival (Kitahata MM, et al. *J Gen Intern Med.* 2003;18:95-103). A prospective cohort study by Heslin and colleagues showed that African-American, Alaskan Native, Native American, Asian, and Pacific Islander patients were less likely to have an infectious diseases specialist compared with Caucasian patients (Heslin KC, et al. *J Gen Intern Med.* 2005;20:283-389). Latino patients were more likely than others to have physicians whose HIV caseload was 24% higher than the physicians of white patients, suggesting that this subpopulation had access to physicians with HIV expertise. Factors associated with having a specialized provider include being a woman, having children in the home, having a case manager, and having a cohort of supportive friends.

When patients are linked with care, adherence is crucial to optimizing clinical outcomes.

El-Sadr reminded providers that adherence is a complex issue that requires establishing a relationship built on trust. In a cohort of HIV-infected prisoners, mistrust of physicians (OR, 0.08), social isolation (OR, 0.08), and mistrust of HIV medication (OR, 0.30) all had a significant impact on adherence (Altice FL, et al. *J Acquir Immune Defic Syndr.* 2001;28:47-58).

El-Sadr concluded, "We have all worked together to build a mosaic of services that provide people with HIV with what they need. Primary care, women's health, harm reduction, peer programs, nutrition, outreach, mental health, social support, and research all form tiles of this fragile mosaic. Our challenge is to maintain and build upon this mosaic to achieve optimal outcomes for all of our patients." ●

Table. Post-test Counseling Rates Following HIV Testing

	Rapid Testing	Traditional Testing
Infected	89%	11%
Uninfected	93%	40%

Liang et al. AIDS Patient Care STDS. 2005.

Measuring Adherence to HIV Medications

Neither pager reminders nor personal visits with pharmacists seemed to boost adherence to an antiretroviral medication regimen among HIV-positive Veterans' Administration patients in San Diego. In fact, patients who relied strictly on a paged reminder, which can come at an inconvenient time, might have poorer adherence than patients who figure out their own medication-scheduling strategies.

These conclusions came from an unpublished study of 291 patients at the VA San Diego Healthcare System. Researchers compared the effectiveness of routine medication counseling to a paged reminder system or a series of four focused, in-person counseling visits with a pharmacist. Adherence was monitored with a computerized medication event monitoring system imbedded in the cap of the prescription vial. Downloadable data in the chip were recorded when the vial cap was opened.

In all three strategies, medication adherence started low (77% versus a target adherence rate of 95%) and remained low during the course of the study, reported University of California San Diego associate professor Allen L. Gifford, MD. Patients in the control group even occasionally outperformed those who received pages or visits. The interventions had no impact on the length of time to treatment failure or whether treatment produced viral suppression.

These results suggest to Gifford a shift in how clinicians should research and implement medication adherence programs. Gifford further observed that medication guidance should be targeted not only to patients who need it, but also to those who are likely to benefit. "Some patients need intervention, but are not ready for it," he said. Gifford recommended medication adherence strategies that are longer and more intensive than the "relatively modest" four visits provided in the VA study. "This strategy would more effectively use providers' time, rather than trying to help patients who are not receptive to behavior change interventions."

To support his suggestions, Gifford pointed to preliminary analyses of two intermediate endpoints in the VA study. Patients who received all four visits prescribed in the study were more likely to adhere to their medication regimens. Another preliminary conclusion suggested that some patients were more likely than others to benefit from an intervention. In the VA study, antiretroviral naïve patients were more likely to follow a medication regimen. "Our hypothesis is that they were really motivated." ●

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